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Comment on the Article: Subretinal Bleb of Voretigene Neparvovec

To the Editor:

We studied with great interest the article Subretinal Bleb of Voretigene Neparvovec by João Pedro Marques et al.[1] Demonstrating new ways of sub-retinal bleb formation in the process of voretigene neparvovec application provides important upgrades of the surgical technique.[1] However, we would like to address some potential bias of the surgical protocol that may confound the final outcomes and propose an alternate approach based on our own experience. We hypothesize that performing only one bleb in the process of subretinal voretigene application, following a saline prebleb, could lead to perifoveal chorioretinal atrophy. Utilizing saline in the process of pre-bleb formation, dilutes the concentration of the vector and possibly lowers the risk of toxicity[2] but calls the efficacy in question on the other hand. The concept of creating only a single bleb and accordingly, instilling the total volume of the drug subretinally, carries a higher risk of foveal rupture due to uncontrolled and excessive retinal stretching. Furthermore, completely detached fovea could be mis-located during the ensuing process of subretinal voretigene neparvovec resorption. Thus, to deliver the total amount of the prescribed volume, it seems rational to distribute it to more than a single bleb. Performing more than one bleb lowers the volume of voretigene neparvovec within a single bleb, and additionally, prevents the detachment of the fovea. Finalization with a fluid-air exchange in the vitreous cavity provides both tamponade and allows a gentler and more favorable subretinal spreading of the drug into the subfoveal space compared to dynamically robust separation of the retinal neuroepithelium by subretinal instillation of the total drug volume in a single shot either manually or by subretinal injector with viscous fluid injection.

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Response to "Comment on the Article: Subretinal Bleb of Voretigene Neparvovec"

In Reply:

We appreciate the authors' comment to our manuscript[1] and share the authors' concern about the development of chorioretinal atrophy following the administration of voretigene neparvovec (VN), as described by Gange et al.[2] In our article, the procedure of subretinal administration of VN was described according to the protocol used in the phase 3 trial that led to the approval of VN[3] by the Food and Drug Administration in the US and European Medicines Agency in Europe. In our limited experience (12 eyes, 6 patients) with VN, the fovea was detached in all cases and the full amount of VN was manually injected subretinally via a single bleb. We did not observe any cases of chorioretinal atrophy so far but we have a limited follow-up (4.00 ± 2.28 months) and an older cohort (27.5 ± 7.82; min 16 – max 39 years old) than Gange et al.[2] Although we can understand the rationale for distributing the drug volume to more than a single bleb, we must keep in mind that this is associated with increased surgical risks due to the need of more than one retinotomy. Furthermore, there is no concluding evidence that detaching the fovea during subretinal injection has a negative impact on the visual function outcomes. In fact, real-world evidence with VN recently published by Sengillo et al[4] showed that no significant difference in

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best-corrected visual acuity change or in central foveal thickness change was found between eyes with and without foveal detachment at any follow-up visit. The phase 3 results at 3 and 4 years[5] showed a similar safety profile as previously described[3] and no cases of cho-rioretinal atrophy in the study participants. We agree that surgical techniques should be perfected to benefit our patients but significant protocol deviations that are not adequately validated may put the drug efficacy and ultimately our patients' vision at stake. As the number of VN treatments increase worldwide, we will be able to evaluate long-term post-market real world outcomes data and hopefully identify the reasons behind the progressive chorioretinal atrophy described by Gange et al.[2]

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Comment on "Lessons Learned From School-Based Delivery of Vision Care in Baltimore, Maryland"

To the Editor:

We read a recently published article by Collins et al[1] on experiences from school-based eye screening with great interest. We would like to share our experiences in pediatric eye screening from India. The pediatric eye screening at our hospital is divided into school, preschool, and newborn screening. School screening focuses on children aged 5 to 18 years, and teachers form the backbone of this endeavor. Preschoolers' screening focuses on ages 6 months to 6 years. The primary aim is to screen for ocular diseases and educate parents and Integrated Child Development Scheme (ICDS) workers about the prevention and treatment of common nutritional deficiencies, ocular diseases, and safety protocols. Newborn screening focuses on retinopathy of prematurity (ROP) screening and targets preterm born babies in the nurseries and neonatal intensive care units.

The school screening has been modified in a very innovative and simple way. We tried 2 models, "All Class Teacher" (ACT) and "Selected Teacher" (ST).[2] In these models, the teachers are trained to prescreen and identify children with a visual acuity of $\leq 20/30$ in either eye or apparent ocular abnormalities before the actual ophthalmic screening. The ophthalmic team then examines these referred children and prescribes spectacles, medical management, or refers to the base hospital for further evaluation as and when needed. In a study by Priya et al,[2] 39,357 children were screened by ACT (761 teachers), and 38,469 children were screened by ST (156 teachers). They found that the ACT model resulted in more efficient screening than ST, at about one-third of the cost, and showed better compliance with hospital referrals. The cost of screening per child with ocular pathology was estimated at $1.91 for ACT and $4.83 for ST.

The preschool screening has been modified since 2015, wherein trained fieldworkers screen children at ICDS centers and kindergarten schools with the help of Plusoptix S12-C photoscreener. In case of a failed result, readings are repeated thrice, and any child failing the results after 3 attempts is referred for examination by the ophthalmic team. We found the sensitivity and specificity of this screening methodology as 86.76% and 82.27%, respectively.[3] For children younger than 3 years, this was 89.19% and 81.18%, respectively.

India is reported to have the largest number of premature babies.[4] With improving neonatal care facilities, the survival rate of premature babies has beaucouped worldwide. Retinopathy of Prematurity Eradication Save Our Sight (ROPE-SOS) is a telescreening project operating since 2015. Trained technicians visit suburban and rural areas and capture fundus images of preterm babies in the neonatal intensive care units/nurseries with RetCam. These images are forwarded to the base hospital, where a diagnosis is given and further

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